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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/617,116 07/14/00 AGHI

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EXAMINER

HM12/0829

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ART UNIT

PAPER NUMBER

1632

DATE MAILED:

08/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	09/617,116	Applicant(s)	AGHI ET AL.
Examiner	Quang Nguyen	Art Unit	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on ____.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) Claim(s) ____ is/are allowed.
- 6) Claim(s) 1-11 is/are rejected.
- 7) Claim(s) ____ is/are objected to.
- 8) Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on ____ is/are: a) accepted or b) objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on ____ is: a) approved b) disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. ____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 4) Interview Summary (PTO-413) Paper No(s) ____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____

DETAILED ACTION

Claims 1-11 are pending in the present application and are examined on the merits herein.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 7-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the *invention*. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

Applicant's invention is drawn to a method for killing neoplastic cells comprising infecting the neoplastic cells with a vector comprising an FPGS gene, followed by treating the neoplastic cells with a chemotherapeutic agent that is activated by the

product of the FPGS gene, and killing the neoplastic cells. Apart from the disclosure of utilizing antifolate drugs that are capable of being polyglutamated by the FPGS gene product to enhance their cytotoxicity or increasing their therapeutic efficacy such as methotrexate, edatrexate, the instant specification fails to teach any other chemotherapeutic agents (small organic organic compounds, peptides, polypeptides, nucleic acids or carbohydrates) that are capable of being activated by the FPGS gene product to effect the killing of neoplastic cells. Additionally, at the effective filing date of the present application the art does not provide such teachings in this regard. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification, and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot fully envision the detailed structure of any and all chemotherapeutic agents that are activated by the encoded FPGS gene product, apart from the antifolate drugs that are substrates of the FPGS gene product and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v.*

Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) A method for killing neoplastic cells *in vitro*, said method comprising: (a) transforming or transfecting said neoplastic cells with a vector comprising a DNA sequence encoding a folylpolyglutamate synthetase (FPGS) operably linked to a promoter, wherein the FPGS is expressed in the neoplastic cells; (b) treating the neoplastic cells of step (a) with an antifolate drug that is capable of being polyglutamated by the FPGS; whereby the neoplastic cells are killed and wherein said vector is a non-viral vector or a replication defective viral vector;

(2) A method for killing neoplastic cells of solid tumors *in vivo*, said method comprising: (a) direct innoculation of said neoplastic cells with a vector comprising a DNA sequence encoding a folylpolyglutamate synthetase (FPGS) operably linked to a

promoter, wherein the FPGS is expressed in the neoplastic cells; (b) treating the neoplastic cells in step (a) with an antifolate drug that is capable of being polyglutamated by the FPGS; whereby the neoplastic cells are killed and wherein said vector is a non-viral vector or a replication defective viral vector;

does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claims are drawn to a method for killing neoplastic cells, said method comprising: (a) infecting said neoplastic cells with a vector for gene delivery, said vector comprising an FPGS gene; (b) treating said neoplastic cells with a chemotherapeutic agent that is activated by the product of said FPGS gene; and killing said neoplastic cells; the same method wherein said FPGS gene is a mammalian gene, preferably a human gene or wherein said chemotherapeutic agent is an antifolate drug, preferably methotrexate, edatrexate, aminopterin or a thymidylate synthetase inhibitor or wherein said vector is a viral vector or a non-viral vector.

The specification teaches by exemplification showing that in comparison with parental 9L rat gliosarcoma cells, 9L/FPGS cells stably transfected with a plasmid vector comprising a human FPGS cDNA are more sensitive to the antifolate drugs such as methotrexate, edatrexate and aminopterin in cell cultures in 4-hour pulses of antifolates. Additionally, the specification teaches subcutaneous implanted 9L/FPGS tumors in nude mice also respond well to the treatments of methotrexate and edatrexate. Applicants further disclose a bystander killing effect of non-transfected tumor cells was observed in both *in vitro* and *in vivo* resulting from the release of antifolates by transfected tumor cells after the removal of extra-cellular drugs.

The above evidence has been noted and considered. However, the specification is not enabled for the instant broadly claimed invention for the following reasons.

The instant claimed invention encompasses both *in vitro* and *in vivo* methods of killing neoplastic cells utilizing a vector comprising an FPGS gene and a chemotherapeutic agent that is activated by the FPGS gene product to effect the killing of the neoplastic cells. The broad claims encompass any and all chemotherapeutic agent that is activated by the FPGS gene to enhance its cytotoxic or therapeutic effects with respect to killing neoplastic cells. The present specification is not enabled for the full scope of the method as claimed for the reason set forth in the Written Description section above. Given the lack of guidance provided by the instant specification regarding to any other chemotherapeutic agent other than the antifolate drugs that are substrates of the FPGS gene product, it would have required undue experimentation for one skilled in the art to make and use the method as claimed.

With respect to the *in vivo* aspect of the claimed method, the nature of the claimed invention falls within the art of *in vivo* gene therapy which at the effective filing date of the present application remains to be unpredictable. Dang et al. (Clin. Cancer Res. 5:471-474, 1999) noted that further advancement in all fields such as gene delivery, gene expression and host immune manipulation is needed to make gene therapy a reality. Dang et al. also pointed out several factors limiting an effective human gene therapy, including suboptimal vectors, the lack of a stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors and most importantly an efficient gene delivery to target tissues or cells (last paragraph, col. 2, page 474). The instant claims encompass any and all routes of delivering a vector comprising an FPGS gene into neoplastic cells *in vivo*. However, vector targeting *in vivo* to desired cells or tissues, for this instance neoplastic cells, for achieving therapeutic effects continues to be unpredictable and inefficient. This is supported by numerous teachings in the art. As examples, Miller & Vile (FASEB 9:190-199, 1995) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances ... Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998) indicated that one of the main obstacles hampering a successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period

of time." (page 53, first paragraph). Deonarain also reviewed new techniques under experimentation in the art which show promises. One of which is the ligand-targeted receptor-mediated vector approach with a relatively higher level of tissue specificity than viruses can offer. However, this approach to gene therapy is much less efficient than viral gene delivery (column 1, last paragraph, page 65). Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy, and the problems which are associated with each. They also indicated clearly that resolution to vector targeting *in vivo* had not been achieved in the art (see the entire article). Verma & Somia also discussed the role of the immune system in inhibiting the efficient targeting of viral vectors such that an efficient expression is not achieved (see page 239, and second and third columns of page 242). Verma & Somia also indicated that appropriate enhancer-promoter sequences can improve expression, but that the "search for such combinations is a case of trial and error for a given cell type." (page 240, sentence bridging columns 2 and 3). The instant specification fails to teach one skilled in the art how to overcome the unpredictability for *in vivo* vector targeting, such that an efficient transfer and expression of a FPGS gene could be achieved in neoplastic cells of solid or non-solid tumors through any and all routes of delivery such that upon treatment with a chemotherapeutic agent, the agent is activated by the FPGS gene product to effect the killing of said neoplastic cells. The exemplification demonstrating the sensitivity of 9L/FPGS rat gliosarcoma cells stably transfected *in vitro* with a plasmid vector comprising a human FPGS cDNA to treatments of antifolate drugs such as methotrexate, edatrexate is not deemed to be sufficient guidance for one skilled

in the art for overcoming the unpredictability of *in vivo* vector targeting to attain therapeutic effects. As such, with the lack of sufficient guidance provided by the present specification, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Regarding to the *in vivo* aspect of the method as claimed, the instant claims encompass the use of replication competent viral vectors. Neither the instant specification nor the prior art at the effective filing date of the present application teaches the use of replication competent viral vectors such as retrovirus, adenovirus or lentivirus (HIV-1 and HIV-2) for achieving therapeutic results via gene therapy. It is unclear whether the treated individual having neoplastic cells succumbs to the cytotoxic effects of replication competent viral vectors prior to any therapeutic effects contemplated by Applicants could be attained by the method as claimed. Furthermore, neoplastic cells infected with replication competent viruses could be lysed prior to any effective accumulation of polyglutamated antifolates could be attained to effect the killing of neoplastic cells as contemplated by the present invention. With the lack of guidance provided by the specification regarding to this embodiment of the claims, it would have required undue experimentation for a skilled artisan to make and use the full scope of the present invention.

The instant claims encompass the use of mammalian artificial chromosome as a non-viral gene delivery of FPGS gene for killing neoplastic cells. However, the instant specification fails to provide any specific teachings regarding to the making or using of any mammalian artificial chromosome for killing a neoplastic cell in a method as

claimed. Furthermore, with respect to the issue of mammalian artificial chromosome, Calos (TIG 12:463-467, 1996; PTO-1449, AT2) noted that "a vector of this size is far beyond the size of vectors in current use for gene therapy and poses problems of major dimensions, particularly for the manufacture and delivery of vector DNA. Therefore, while construction of artificial chromosome vectors has not yet been realized, once it is, a series of challenging technical barriers will have to be surmounted before such molecules could reasonably be used as gene therapy vectors" (page 464, col. 2, last paragraph). Therefore, with the lack of guidance provided by the instant specification it would have required undue experimentation for a skilled artisan to make and use this embodiment of the claimed invention.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability of the gene therapy art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 and its dependent claims, the phrase "said neoplastic cells" in steps (b) and (c) is unclear. Which neoplastic cells? The ones that are infected with a vector for

gene delivery or the non-infected ones. Additionally, it is noted that as recited in step (a), there is no requirement that neoplastic cells infected with a vector comprising an FPGS gene express the FPGS gene product. As such, how can an administered chemotherapeutic agent be activated? Furthermore, it is unclear what is encompassed by the phrase "an FPGS gene". This is because it is not clear what is the beginning or the end of an FPGS gene. The metes and bounds of the claims can not be clearly determined. Clarification is requested.

In claim 11, the phrases "the direct injection of nucleic acid", "particle-mediated gene transfer", "receptor-mediated gene transfer" render the claim indefinite. This is because the phrases indicate routes or methods of gene delivery and not to a non-viral vector as recited in claim 10 from which claim 11 is dependent upon. It is also unclear why "DNA-adenovirus conjugate" is considered to be a non-viral vector because clearly it contains a virus component, adenovirus. Additionally, it is unclear what is encompassed by the phrases "endothelial cell" and "macrophage". Why should these cells be considered as non-viral vectors? How can an administration of an endothelial cell or a macrophage result in an infection of neoplastic cells with a vector comprising an FPGS gene? It should be noted that the base claim 1 is directed specifically to a method comprising an infection of neoplastic cells with a vector comprising an FPGS gene in both *in vitro* and *in vivo*. With respect to the *in vivo* aspect of the base claim, its nature belongs to an *in vivo* gene therapy art and not to an *ex vivo* gene therapy art. Clarification is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (J. Biol. Chem. 268:21680-21685, 1993; PTO-1449, AS) as evidenced by Osborne et al. (J. Biol. Chem. 268: 21657-21664; 1993) and in view of Garrow et al. (Proc. Natl. Acad. Sci. 89:9151-9155, 1992; PTO-1449, AR) and Roth & Cristiano (J. Natl. Cancer Inst. 89:21-39, 1997; PTO-1449, AT).

The claims are drawn to a method for killing neoplastic cells, said method comprising: (a) infecting said neoplastic cells with a vector for gene delivery, said vector comprising an FPGS gene; (b) treating said neoplastic cells with a chemotherapeutic agent that is activated by the product of said FPGS gene; and killing said neoplastic

cells; the same method wherein said FPGS gene is a mammalian gene, preferably a human gene or wherein said chemotherapeutic agent is an antifolate drug, preferably methotrexate, edatrexate, aminopterin or a thymidylate synthetase inhibitor or wherein said vector is a viral vector or a non-viral vector.

With respect to the enabled scope of the present invention, Kim et al. teaches that Chinese hamster ovary (CHO) cells expressing human folylpolyglutamate synthetase (FPGS) metabolize methotrexate (MTX) to polyglutamates characteristics of human cells (see Table I, page 21681), and that upon a short term exposure to MTX (4 h), cells expressing higher levels of human FPGS are more sensitive to the cytotoxicity of MTX (see Table III, page 21682). The CHO cells expressing human FPGS have been obtained by the co-transfection of CHO cell mutant (AUXB1) with sheared bulk human DNA and pSV2-neo plasmid as evidenced by the teachings of Osborne et al. from the same research group (see page 21658, col. 2, last full paragraph). Kim et al. noted that the ability of cells to metabolize MT to longer chain length derivatives enhances cytotoxicity when MTX is infused for a limited period and then removed, which mimics clinical usage, and that larger effects of FPGS activity levels on the cytotoxicity of antifolates that require polyglutamylation for effective inhibition of target enzymes were also observed (page 21683, col. 2, last paragraph). Kim et al. further teach that lowered FPGS activity may be a general mechanism by which cells (e.g. human leukemia cells) can become resistant to a wide range of antifolates (page 21684, col. 1, top 5 lines) and that decreased polyglutamylation as a mechanism for inherent MTX resistance for a number of sarcoma and squamous carcinoma cell lines even

though FPGS levels appear normal (page 21684, col. 1, bottom of the second paragraph). Kim et al. do not specifically teach the transformation or transfection of neoplastic cells with a vector comprising a DNA sequence encoding FPGS, followed by a treatment of an antifolate drug to effect the killing of said neoplastic cells.

However, Garrow et al. teach the cloning of a human cDNA sequence encoding for FPGS, as well as the expression of human FPGS in mammalian CHO AUXB1 cells with a plasmid vector pSVK-hFPGS (see Fig. 1 and page 9152, col. 2, first full paragraph). Furthermore, Roth & Cristiano review various gene therapy approaches utilizing viral and non-viral vectors that have resulted in the regression of tumors *in vivo* (see the entire article, especially, the section of Drug-sensitivity genes on pages 22-23). With respect to clinical applications, Roth & Cristiano further noted that the administration of viral vectors to patients is limited to intratumoral delivery since the available vectors have not been approved for systemic administration (page 24, col. 1, last paragraph continues to top of col. 2).

Accordingly, at the time of the instant invention it would have been obvious and within the skills of an ordinary skilled artisan to modify the method disclosed by Kim et al. by transfecting or transforming a non-viral vector or a replication-defective viral vector comprising a DNA sequence encoding FPGS into neoplastic cells *in vitro* or locally to neoplastic cells in a tumor *in vivo* in view of the teachings by Garrow et al. and Roth & Cristiano to enhance the effective cytotoxic effects of antifolate drugs. One of ordinary skilled in the art would have been motivated to carry out the above modification with a reasonable expectation of success because on the basis of their findings, Kim et

al. noted that the ability of cells to metabolize MT to longer chain length derivatives enhances cytotoxicity when MTX is infused for a limited period and then removed, which mimics clinical usage, and that larger effects of FPGS activity levels on the cytotoxicity of antifolates that require polyglutamylation for effective inhibition of target enzymes were also obtained (page 21683, col. 2, last paragraph). Furthermore, as taught by Kim et al., lowered FPGS activity and decreased polyglutamylation of antifolates may be general mechanisms by which cancer cells become resistant to a wide range of antifolates. The production and cloning of replication defective viral vectors and non-viral vectors comprising a cDNA sequence encoding FPGS are methods common to molecular biology and the *in vivo* aspect of the present invention would have been within the scope of skills of an ordinary artisan at the time of the instant invention as evidenced by the teachings of Roth & Cristiano.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Art Unit: 1632

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 308-8724.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Quang Nguyen, Ph.D.


DAVET. NGUYEN
PRIMARY EXAMINER